because of the well settled acceptance of the term "about" in claim language. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983).

The Office Action rejects claim 24 because, it asserts, claim 1 does not provide sufficient antecedent basis for the possibility of a linker comprising a detectable or therapeutic radionuclide. While Applicant respectfully disagrees with the rejection, out of a spirit of cooperation in order to have the case more promptly allowed, Applicant has amended claim 1 to expressly provide antecedent basis.

Rejections Under 35 U.S.C. 103

The Office Action rejects claims 1 and 9-12 for allegedly being obvious over Collins et al. (US 6,004,533) in view of Schinazi et al. (US 5,599,796). Collins et al. disclose a process for imaging tissues and organs in vivo by conjugating a diagnostic radionuclide to vitamin B12 and administering the conjugate to a subject. The process relies upon the fact that tumor cells overexpress cell surface receptors for transcobalamin (which acts as a protein carrier for vitamin B12). Thus, by systemically administering to a patient vitamin B12 linked to a imaging radionuclide, and subsequently imaging all or a portion of the patient's body, a radiologist is able to identify tumors in tissues and organs in the body.

Boron neutron capture therapy ("BNCT") is not a diagnostic technique; it is a two step method of therapy that requires (1) administration of boron-10 containing material, and (2) administration of a source of neutrons that causes the decay of the boron-10 with release of destructive energy. Collins et al. do not address BNCT in their disclosure. Indeed, in a lengthy presumably comprehensive paragraph, Collins et al. set out numerous detectable agents and omits boron-10. (See column 5, line 61, through column 6, line 20). Collins et al. also do not disclose that vitamin B12 could, if used as a therapeutic targeting agent, deliver sufficient boron to treat cancer in a BNCT regimen.

Schinazi et al. disclose the use of boron neutron capture therapy to treat urogenital cancers. Schinazi et al. further disclose various carriers for the boron including carboranyl-containing nucleosides and oligonucleotides. (Col. 6, lines 21-24). Importantly, "any boron containing compound that is sufficiently lipophilic to pass through the appropriate urogenital membranes in a quantity high enough to achieve therapy on irradiation with low-energy neutrons

can be used." (See Abstract). Schinazi et al. thus disclose the use of lipophilic compounds to facilitate entry of boron-10 into tumor cells. BNCT therapy is localized by pointing the neutron beam toward the desired location on a patient's body.

Taken together, these references do not support a prima facie case of obviousness because they would not have motivated a skilled worker to use vitamin B12 as a carrier for boron in BNCT.

1. The references do not support a prima facie case of obviousness because a skilled worker would not be motivated to use vitamin B12, which is known to be an extremely hydrophilic molecule, as the delivery vehicle in Schinazi's lipophilic delivery system.

Schinazi et al. state in several locations throughout their patent that "any boron containing compound that is sufficiently lipophilic to pass through the appropriate urogenital membranes in a quantity high enough to achieve terapy on irradiation with low-energy neutrons can be used." See Abstract and col. 6, lines 14-17. Schinazi et al. then provide several pages of disclosure relating to how to manipulate the lipophilicity of boron modified compounds. See columns 10-17. The plain focus of Schinazi et al. was thus on lipophilic delivery systems.

Vitamin B12, however, is well known for its hydrophilicity and water solubility. See attached article from the Indian Journal of Pharmaceutical Sciences. Indeed, the Merck Index (12^{th} Edition) reports that 1 gram will dissolve in a mere 80 milliliters of water. Vitamin B12 is not a lipophilic molecule.

Because Schinazi et al. teach the necessity of lipophilic boron-10 carriers in BNCT regimens, they teach away from the use of vitamin B12 in BNCT.

2. The references do not support a prima facie case of obviousness because a skilled worker would not be motivated to use a receptor-dependent delivery vehicle in Schinazi's lipophilic delivery system.

As explained in the background of the specification, vitamin B12 is delivered to cells in a two step process: (1) the vitamin B12 binds a transcobalamin transport protein in serum, and (2) the transcobalamin protein binds to a transcobalamin receptor on the surface of the cell. Vitamin B12 uptake by tumor cells is thus a receptor mediated event.

This is in contrast to lipophilic mediated transport of uptake into lipophilic membranes or materials. The Schinazi et al. patent teaches that increased lipophilicity of the boron-10 bearing compound causes preferential uptake in liposomal materials. Because Schinazi et al. emphasize the need for a lipophilic boron-10 delivery system in their patent, a skilled worker would not be motivated to substitute a delivery system based upon vitamin B12 that relies upon a receptor-uptake mechanism..

3. The references do not support a prima facie case of obviousness because a skilled worker would not expect to successfully employ vitamin B12 as the delivery vehicle in Schinazi's BNCT regimen.

A skilled worker also would not be motivated to use vitamin B12 as a carrier in a BNCT regimen because there is nothing in the references to impart a reasonable expectation of success using vitamin B12. In particular, nothing in the references indicates that vitamin B12 would deliver sufficient boron to an affected tumor to allow BNCT to be effectively carried out. Before vitamin B12 can enter a cell, it must first bind to a transport protein (transcobalamin), and the vitamin B12/transcobalamin conjugate must then bind a transcobalamin receptor on the cell surface before it is transported into the cell. The rate and extent of vitamin B12 uptake is constrained by the availability of transcobalamin carrier proteins in serum, and the number of transcobalamin receptors present on the cell surface. Both of these events (transcobalamin binding and receptor mediated endocytosis) represent significant barriers to the ultimate success of vitamin B12 as a carrier in BNCT, and keep a skilled work from predicting a reasonable expectation of success.

Because lipophiles do not necessarily depend on cell surface receptor for their entry into the cell, lipophile-mediated BNCT is able to enhance the quantity of BNCT taken up by tumor cells. The objective of Schinazi's lipophile mediated BNCT regimen was to maximize the quantity of boron delivered to the tumor cells, as opposed to maximizing the selectivity of tumor cell uptake. This is evident from the fact that BNCT therapy is optimized when the ratio of boron in a tumor and serum is up to about 2:1. (Col. 7, line 32). Schinazi et al. could get away with such a rough uptake into tumor cells because the therapy would be localized by the neutron beam to a well-defined tumor target.

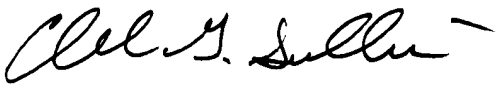
In contrast, the diagnostic techniques disclosed by Collins et al. rely upon a highly selective mechanism in which serum radionuclide must be minimized to prevent background interference with the quality of the image obtained. In an imaging system, the selectivity of the delivery system thus takes on much greater importance than it takes in a delivery system such as Schinazi's, wherein the bulk capacity of the delivery system appears to take on paramount concern. The advantage of using vitamin B12 in Collins' process is the preference of vitamin B12 for cancer cells over non-cancer cells; but this advantage is substantially diminished in BNCT therapy because the BNCT therapy can be localized by properly focusing the neutron beam.

Therefore, the fact that Collins et al. showed that vitamin B12 could achieve such a high level of selectivity would not lead a skilled worker to believe that vitamin B12 could also be used in a BNCT regimen because it says nothing about the quantity of boron that could be delivered using vitamin B12, and Schinazi et al. teach that quantity is an important element for any successful BNCT regimen.

Conclusion

Based upon the foregoing amendments and arguments, Applicants respectfully submit that this application is now in condition for allowance and earnestly solicit prompt notification to that effect.

Respectfully submitted,



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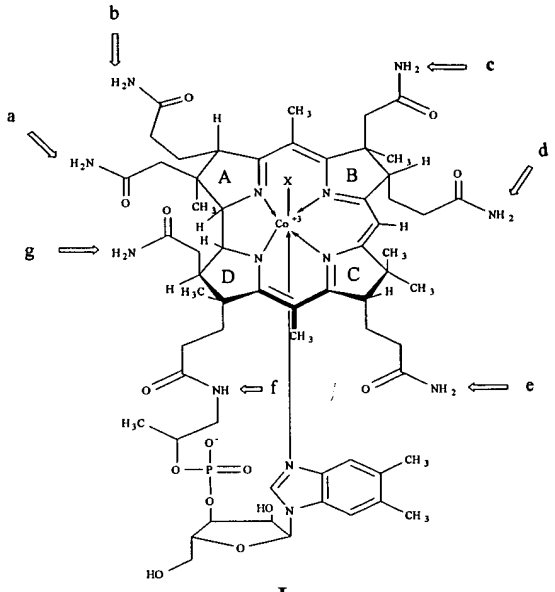
Version with Markings to Show Changes Made

Claims 1 and 9 have been amended as follows:

1. (Thrice Amended) A [residue of a] compound of formula I:



I

linked to [a residue of] a molecule comprising B-10, wherein X is CN, OH, CH_3, adenosyl or a molecule comprising B-10 **and optionally linked to a linker comprising a detectable radionuclide or a therapeutic radionuclide**; or a pharmaceutically acceptable salt thereof.

9. (Once amended) The compound of claim 1, wherein the molecule comprising B-10 contains **[about]** 1 to about 20 boron atoms, inclusive.